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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/374,213	08/13/1999	DAVID STERN	59472/JPW/SH	3469

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/374,213	STERN ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,44,46 and 55-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41,44,46 and 55-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 August 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid.

The amendment filed 18 August 2003 has been entered. Claims 1-40, 42, 43, 45 and 47-54 were cancelled by the Applicant.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 41, 44, 46 and 55-58 are currently under examination.

Claim Rejections/Objections

Claim objections

Claim 55 is objected to for reciting or encompassing non-elected inventions - e.g., "a bone marrow cell."

Claim rejections- 35 USC §103, obviousness

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 41, 44, 46, 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan, et al (PNAS, 1997, 94: 5296) in view of Hale, et al (Cytokine, 1 995, 7: 26) and Heaney, et al (Blood, 1993, 82: 1 945). Yan et al teach that amyloid beta peptide binds to the receptor for RAGE. They also demonstrate that binding of amyloid to the RAGE receptor induces oxidative stress, activation of microglia, and activation of inflammatory pathways involving transcription factor NF-kB. They further suggest that these processes may contribute to the cellular pathologies seen in Alzheimer's Disease. They do not teach inhibition of this binding event. Hale, et al, teach inhibition of tumor necrosis factor using the soluble form of its receptor. Elevated levels of TNF are significant in the pathology of sepsis and the circulatory collapse that

can result from severe sepsis. Soluble receptors for TNF were shown to be effective in inhibiting the binding of TNF to the cell-surface receptors. Soluble TNFR's were also effective in inhibiting the effects of TNF in culture as well as in several models of sepsis in mice and baboons (p. 27 and 33). They further suggest that endogenous "soluble receptors may be part of a negative feedback mechanism to inhibit the biological effects of TNF". In fact, Heaney and Golde give numerous examples in which soluble receptors are involved in intercellular signaling (p. 1 946, for example). They discuss the consequences of such signaling to disease states, and suggest multiple roles for soluble receptors: for example, to temporarily inhibit or confer sensitivity to a ligand (p. 1 947). They conclude their discussion by stating that "construction and development of soluble receptors as pharmaceuticals may be useful to specifically inhibit or facilitate hormone action in disease states." It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the soluble form of RAGE to inhibit binding of an amyloid peptide that is known to bind the membrane-bound form of RAGE. The teachings of Yan et al, demonstrated binding of β-amyloid to the receptor for AGE on the surface of cells. Binding triggers a cascade of events that may be important in generating oxidative stress in cells expressing RAGE. An obvious way to inhibit such an event is to use the soluble form of the receptor to "out-compete" the endogenous binding. The literature gives examples of soluble receptors and examples wherein disease states have been successfully ameliorated using soluble receptors. The person of ordinary skill in the art would have been motivated to try to inhibit such binding events as those in the instant application. He/she would have reasonably expected success using a soluble form of the receptor to "tie-up" ligand, because he/she knows from the literature that the ligand binds the receptor. Furthermore, there are examples in the literature

where similar methods were used to bind ligand and thus affect the outcome of a disease triggered by a binding event.

35 USC § 112, First paragraph-scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 41, 44, 46 and 55-56 are rejected under 35 U.S.C. 1 12, first paragraph, because the specification, while being enabling for inhibiting binding of β-amyloid to RAGE in vitro, does not reasonably provide enablement for inhibiting binding of amyloid to RAGE in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to the use of soluble RAGE to inhibit binding of amyloid peptide to RAGE. The specification discloses methods for using the soluble receptor for AGE as an inhibitor of binding of a β-sheet fibril to the membrane-bound RAGE. The scope of the patent protection sought by the Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons:
The specification discloses an enabled utility for soluble RAGE as to be used to inhibit binding of amylin, β-amyloid or related peptides to the membrane-bound receptor for AGE in PC12 cells. The specification reads on a curative or preventative therapy for certain dementias such as Alzheimer's disease. However, Alzheimer's disease is a highly complex disorder that may take years to develop (Pearlman, et al. Neurobiology of Disease, pp 307-318, esp. pp 310-311). In

addition, multiple neuronal cell types are involved (pp. 315-317), and several protein types contribute to plaques and tangles (p. 31 6). Despite several lines of research ranging from genetics and immunology to pharmacology and cognitive sciences, and despite the fact that the clinical diagnosis is relatively unambiguous, at least in later stages, Alzheimer's disease is still seen as a largely incurable and untreatable disease (pp. 310-311). Furthermore, there is no discussion in the instant application of how to administer sRAGE in humans and how to measure the clinical effects. There are no discussions of routes of administration, side effects, or dosages needed.

Due to the large quantity of experimentation required to determine how to use soluble RAGE to inhibit amyloidosis in vivo, the Lack of direction or guidance in the specification regarding such (e.g.:, the lack of guidance regarding specific activity of sRAGE in humans), the lack of working examples to same, the state of the art showing the unpredictability of treating dementias, and the breadth of the claims which embrace in vivo methods, undue experimentation would be required pf the skilled artisan to make and use the claimed invention in its full scope.

35 USC § 112, First paragraph-lack of enablement

Claims 57 and 58 are rejected under 35 U.S.C. 112, first paragraph, because the subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for the limitations of the claims wherein a method of inhibiting binding of a peptide that forms amyloid to a membrane-bound receptor for AGE is described. Claims 57 and 58 are drawn to a method of inhibiting binding of an amyloid peptide to a

membrane-bound receptor for AGE. The specification discloses using the soluble form of the receptor to inhibit binding of amyloid to RAGE by concentration-dependent competition binding. Experiments were described in which inhibition of binding between amyloid and RAGE was measured in PC12 cells transfected with RAGE. The disclosure also described applying SRAGE to mouse splenic cells and subsequently measuring the changes in amyloid formation and changes in NFkB and interleukins.

A sufficient amount of direction or guidance is lacking in claims 57 and 58. The specification gives examples wherein binding of amyloid by sRAGE in splenic cells or RAGE - transfected PC12 cells is inhibited in culture. However, nowhere in the specification is a nexus described between inhibition of binding of amyloid and a disease state. The examples are directed to methods of inhibiting binding of an amyloid peptide to RAGE in cultured or isolated cells. Later transduction events are described and measured: specifically the subsequent increase in NFκB and interleukins after binding of amyloid to cells. However the relationship between these early events and disease is poorly understood. In addition, Alzheimer's disease therapy is highly unpredictable, and using the methods described to obtain any clinical effect would require a large amount of experimentation.

In summary, the specification does not provide a description of a repeatable process of inhibiting binding of an amyloid peptide to RAGE on cultured or isolated cells in such a way as to modulate a disease state involving "β-sheet fibrils." In addition, the predictability of the art is very low with regard to the results of inhibiting binding of an amyloid peptide to RAGE in a mammal with a disease involving "β-sheet fibrils" in the manner specified. For this reason undue

experimentation would be required to determine effective methods of inhibiting binding of an amyloid peptide to RAGE to ameliorate a disease state.

Applicants maintain, in response to the Advisory Action (10 April 2003) that there is an art-recognized nexus between a model of amyloidosis in a mouse pancreas and a possible treatment for Alzheimer's disease.

Applicant's arguments (19 August 2003) have been fully considered but are not deemed to be persuasive for the following reasons:

There exist several problems with using mouse models of Alzheimer's disease in which there are defects in amyloid processing to predict whether a therapy in humans will be effective. As discussed above, Alzheimer's disease is a disease of unknown etiology, and cognitive deficits do not necessarily correlate well with amyloid deposition. Additionally, tests of learning and memory in animals cannot be seen to reflect the cognitive deficits seen in humans with Alzheimer's disease. "Higher" motor functions, such as use of language and associative learning, are compromised early in the etiology of AD and in fact, are the defining deficits in the disease (Pearlman, et al, eds, Neurobiology of Disease, p. 311). Such deficits that distinguish Alzheimer's diseases from other amyloid diseases or from more localized causes of cerebral damage (i.e, stroke) cannot be adequately evaluated by means of an animal model.

35 USC § 112, second paragraph-indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41, 44, 46 and 55-58 are rejected under 35 U.S.C. 112, -second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims encompass a method of using SRAGE for preventing the interaction of an amyloid-forming peptide with RAGE. However, one skilled in the art cannot determine the metes and bounds of the claimed invention because there is no recognized structural or functional determinants in the claims such that the molecules encompassed can be distinguished from any other molecule. Aside from the art-recognized names of the molecules used for the claimed invention, there is nothing to distinguish them from similar peptides from other species, nor from mutants and variants.

Conclusion:

Claims 41, 44, 46 and 55-58 are rejected for the reasons cited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (571) 272-0887.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW

7 June 2004

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER